IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#18

APPLICANT:	Lichtenberger, Lenard M.	§	EXAMINER: JIANG
SERIAL NO:	09/827,493	§	GROUP ART UNIT: 1617
FILED:	04/06/01	§	DOCKET: 96606/15UTL
		§	
FOR:	Unique Composition of Zwitterionic Phospholipids and Bisphosphonates with Reduced Toxicity and Enhanced Bioavailability	§	

EV 123 140 689 US Number	CERTIFICATE OF MAIL BY EXPRESS MAIL	February 13, 2003 Date of Deposit

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to the:
Assistant Commissioner of Patent
Washington, D.C. 20231

Robert W. Strozier — February 13, 2003 Date of Signature

RULE 132 DECLARATION

My name is Dr. Lenard M. Lichtenberger and I am over 18 years of age and the inventor of this application. I am submitting this declaration to provide the Examiner with information relating to the ability of bisphosphonates to disrupt a phosphatidylcholine (PC) monolayer - a model for the lining of the GI tract.

I declare as follows:

A technician under my supervision demonstrated that two bisphosphonates, risedronate and pamidronate, have the capability, in a dose-dependent fashion, of reducing the hydrophobicity (as measured by contact angle analysis) of a monolayer of a synthetic PC (diplamitoyl-PC known as DPPC) deposited on a glass slide. I have attached the data in chart form thereto. This data shows that bisphosphonates are effective in disrupting the packing efficiency of PC monolayers and in disrupting the stability of PC even at low concentration.

Because bisphosphonates disrupt the packing and stability of PC monolayers on an inert surface that mimics the lining of the GI tract, one of ordinary skill in the art could have concluded that the addition of PC would have had no effect on bisphosphonate toxicity. Moreover, because bisphosphonates have higher charge density (double the charge) at the phosphate head group, an ordinary artisan would anticipate that bisphosphonates have a higher affinity for the lining of the GI tract than do PCs. Furthermore, because PC are known to form liposomes and/or micelles, and because bisphosphonates have a similar zwitterionic structure, an ordinary artisan could have anticipated that the two compounds would form mixed liposomes

and/or micelles. The formation of such mixed liposomes and/or micelles could increase the bisphosphonate concentration at the mucosal lining of the GI tract, because PC – containing lipoidal suspensions are known to recruit to surfaces, such as the lining of the GI tract, an effect that could result in an increase in the GI toxicity of bisphosphonates.

It is the inability to know in advance how a new combination of pharmaceuticals will behave in animals that makes discoveries in the arena of pharmaceuticals so unpredictable. Moreover, it is only after our research that it became clear that PCs can reduce bisphosphonate toxicity with a concurrent modest enhancement of bisphosphonate bioavailability, results that could not have been proven *a priori*.

I, being hereby warned that willful, false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and that such willful, false statements may jeopardize the validity of the application or any patent maturing therefrom, declare that all statements made of my own knowledge in this Declaration are true and all statements made on information and belief are believed to be true.

Date: **February 13, 2003**

Respectfully submitted,

Lenard M. Lichtenberger